

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 209/52	A1	(11) International Publication Number: WO 93/18001 (43) International Publication Date: 16 September 1993 (16.09.93)
---	-----------	--

(21) International Application Number: PCT/US93/00008

(22) International Filing Date: 7 January 1993 (07.01.93)

(30) Priority data:
844,367 2 March 1992 (02.03.92) US

(60) Parent Application or Grant

(63) Related by Continuation
US 844,367 (CON)
Filed on 2 March 1992 (02.03.92)(71) Applicant (for all designated States except US): PFIZER
INC. [US/US]; 235 East 42nd Street, New York, NY
10017 (US).

(72) Inventor; and

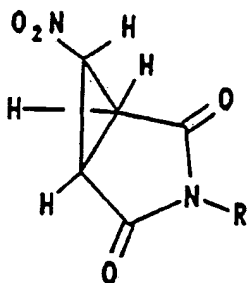
(75) Inventor/Applicant (for US only) : BRAISH, Tamim, F.
[LB/US]; 991 Shewville Road, Ledyard, CT 06339 (US).(74) Agents: RICHARDSON, Peter, C. et al.; Pfizer Inc., 235
East 42nd Street, New York, NY 10017 (US).(81) Designated States: AU, CA, FI, HU, JP, KR, NO, NZ, US,
European patent (AT, BE, CH, DE, DK, ES, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE).

Published

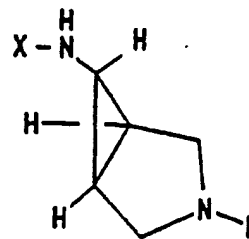
With international search report.

11017 U.S. PTO
10/087756
03/04/02

(54) Title: PREPARATION OF INTERMEDIATES IN THE SYNTHESIS OF QUINOLINE ANTIBIOTICS



(III)



(VII)

(57) Abstract

This invention relates to novel processes for preparing compounds of formulae (III) and (VII) wherein R and X defined as below. Compounds of the formulae (VII) are useful as intermediates in the syntheses of azabicyclo quinoline carboxylic acids having antibacterial activity. This invention also relates to certain novel intermediates in the syntheses such antibiotics.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SK	Slovak Republic
CI	Côte d'Ivoire	LJ	Liechtenstein	SN	Senegal
CM	Cameroon	LK	Sri Lanka	SU	Soviet Union
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	MC	Monaco	TG	Togo
DE	Germany	MG	Madagascar	UA	Ukraine
DK	Denmark	ML	Mali	US	United States of America
ES	Spain	MN	Mongolia	VN	Viet Nam
FI	Finland				

5

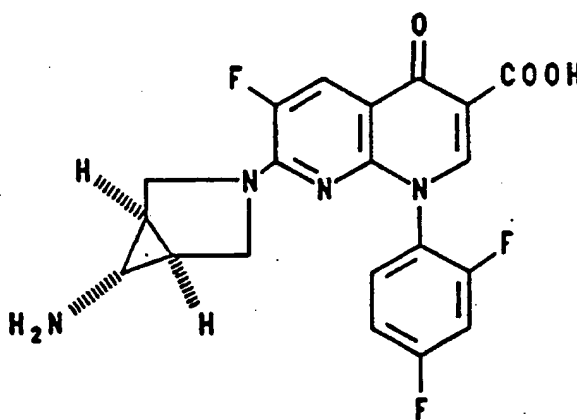
PREPARATION OF INTERMEDIATES IN THE SYNTHESIS
OF QUINOLINE ANTIBIOTICS

Background of the Invention

This invention relates to novel processes for the preparation of intermediates in the synthesis of the quinoline antibiotic 7-(1 α ,5 α ,6 α)-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid and related antibiotic compounds. The quinoline antibiotic 7-(1 α ,5 α ,6 α)-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid has the chemical formula

15

20



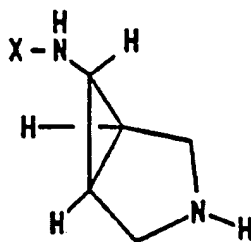
(I)

25 This compound and related azabicyclo quinoline carboxylic acids that exhibit antibacterial activity are referred to in United States Patent Application 07/551,212, filed on July 11, 1990 and World Patent Application WO 91/02526, filed on August 16, 1989 and published on March 7, 1991. Both of the foregoing applications are assigned in common with the present application and are incorporated herein by reference in their
30 entirety.

The novel methods of this invention may be used to prepare compounds of the formula

35

-2-

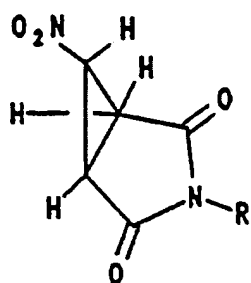


(VII)

which are intermediates in the synthesis of the quinoline antibiotic of the formula I and
 10 the azabicyclo quinoline carboxylic acid antibiotics referred to above. The methods by
 which compounds of the formula VII may be converted into such antibiotic compounds
 are set forth in detail in United States Patent Application 07/551,212 and World Patent
 Application WO 91/02526.

Summary of the Invention

15 The present invention relates to a process for preparing a compound of the
 formula

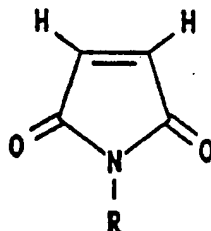


(III)

25

wherein R is (C₁-C₆) alkyl, (C₃-C₆) cycloalkyl or benzyl, wherein the phenyl moiety of said
 benzyl group may be substituted, optionally, with one or more substituents
 independently selected from halo (e.g., chloro, fluoro, bromo or iodo), nitro, (C₁-C₆)
 alkyl, (C₁-C₆) alkoxy, amino and trifluoromethyl, comprising reacting a compound of the
 30 formula

-3-



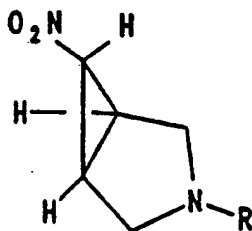
(III)

wherein R is defined as above, with a halonitromethane in the presence of a base.

- 10 In a preferred embodiment of this invention, the compound of formula III formed in the above process is a compound wherein R is (C₁-C₆)alkyl or benzyl. In a more preferred embodiment, R is benzyl.

The term "halo", as used herein, refers to chloro, fluoro, bromo or iodo.

- This invention also relates to the process described above, further comprising
15 reacting the compound of formula III so formed with a reducing agent to form a compound of the formula

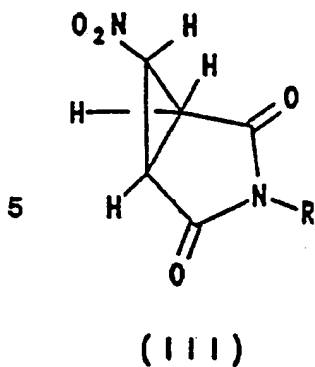


(IV)

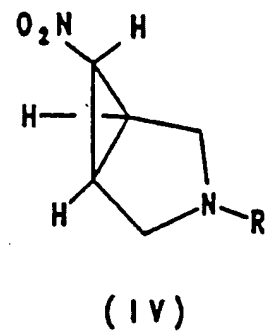
- 25 wherein R is defined as above.

This invention also relates to compounds having the formula

-4-



or



10 wherein R is defined as above.

Detailed Description of the Invention

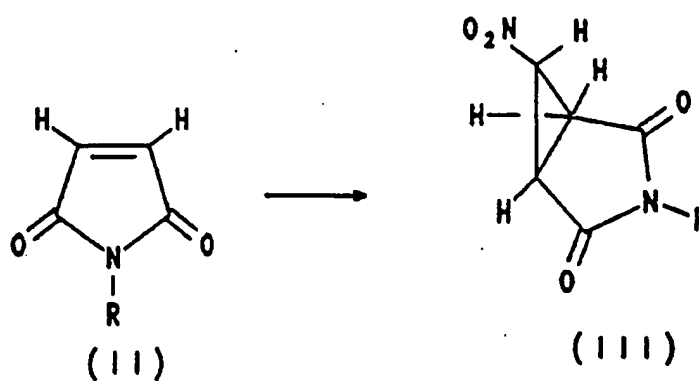
The processes of the present invention and the preparation of the compounds of the present invention are illustrated in the following reaction scheme. Except where otherwise indicated, in the reaction scheme and discussion that follow, formulas I, II,

15 III and IV, and substituents R and X are defined as above.

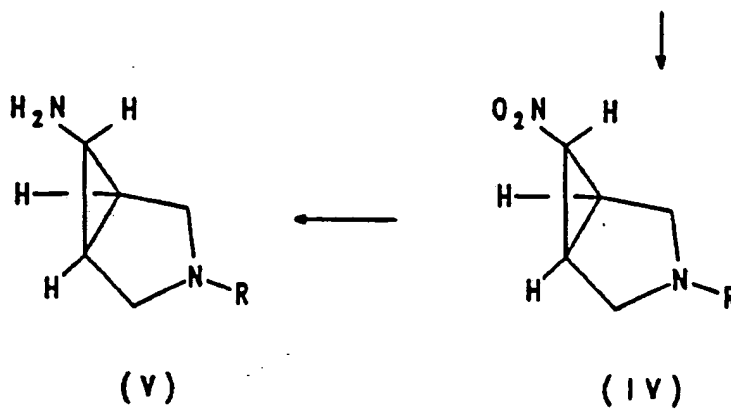
-5-

SCHEME

5

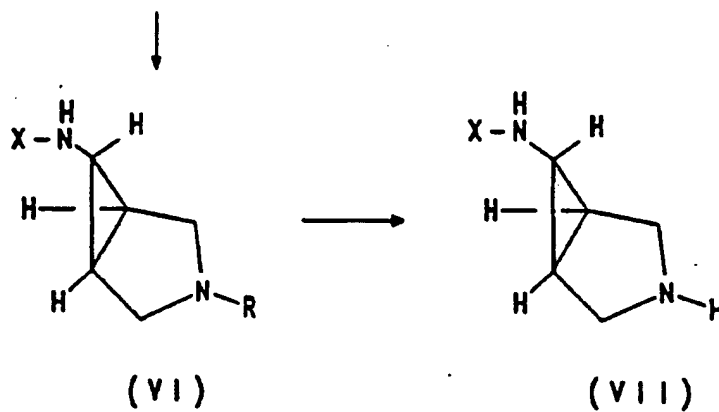


10



15

20



25

30

The above reaction scheme illustrates the preparation of compounds of the formula VII, which are useful intermediates in the synthesis of the quinoline antibiotics referred to above.

Referring to the above scheme, reaction of a compound having formula II with
5 a halonitromethane, preferably chloronitromethane (ClCH_2NO_2) or bromonitromethane (BrCH_2NO_2), in the presence of a base yields the corresponding compound of the formula III. This reaction is generally conducted in an inert, polar, aprotic solvent such as dimethylformamide (DMF), dimethylsulfoxide (DMSO) or dimethylacetamide (DMAC), an inert ethereal solvent such as ethyl ether, glyme or tetrahydrofuran (THF), or another
10 inert solvent such as benzene, toluene or a chlorinated benzene or toluene. Toluene is preferred. Suitable reaction temperatures range from about -78°C to about 80°C , with about 0°C being preferred. It is preferable to add the base last. Examples of appropriate bases include carbonate bases such as potassium or sodium carbonate, phosphorine amide bases such as 2-tert-butylimino-2-diethylamino-1,3-
15 dimethylperhydro-1,3,2-diaza-phosphorine, and amine bases such as triethylamine, guanidine, diisopropylethylamine, tetramethylguanidine, 1,8-diazobicyclo-[5.4.0]undec-7-ene (DBU) and 1,5-diazobicyclo-[4.3.0]non-5-ene (DBN). It is advantageous to use an amine base and, most preferably, to use DBU.

Reduction of the compound of formula III so formed yields the corresponding
20 compound of formula IV. Appropriate reducing agents include borane/dimethylsulfide, borane/THF, sodium borohydride and a borontrifluoride-etherate mixture. The preferred reducing agent is borane/THF. The reduction is typically carried out at temperatures ranging from about 45°C to about 90°C , in an inert ethereal solvent such as glyme, diglyme, diethylether, diisopropyl ether or THF. It is preferably carried out at about
25 66°C in THF.

The resulting compound of the formula IV may be converted into the corresponding amine of formula V by treating it with a metal and an inorganic acid. The preferred metal is zinc. Suitable inorganic acids include hydrochloric acid, sulfuric acid. Hydrochloric acid is preferred. This reaction is generally conducted in a lower
30 alcohol solvent such as ethanol, methanol, 1-propanol or 2-propanol, preferably ethanol, at a temperature from about 0°C to about 80°C , preferably at about 25°C .

The corresponding compound of formula VI, wherein X is a nitrogen protecting group, is then formed by adding a suitable nitrogen protecting group to the unsubstituted amino nitrogen of the compound of formula V. Several well known

nitrogen protecting groups can be used. Such groups include (C₂-C₆) alkoxy carbonyl, optionally substituted benzyloxy carbonyl, aryloxy carbonyl, silyl, trityl, vinyloxy carbonyl, O-nitrophenylsulfonyl, diphenylphosphinyl, p-toluenesulfonyl, and benzyl. It is advantageous to use di-t-butylidicarbonate or 2-t-butoxycarbonyloxyimino-2-phenylacetonitrile. The addition of the nitrogen protecting group is usually carried out in a chlorinated hydrocarbon solvent such as methylene chloride or 1,2-dichloroethane, or an ethereal solvent such as glyme, diglyme or THF, in the presence or absence of a catalytic amount of an amine base such as triethylamine, diisopropylethylamine or pyridine, preferably triethylamine, at a temperature from about 0°C to about 50°C, preferably at about 25°C.

When R is benzyl, the hydrogenolytic removal of the R group from the compound of formula VI formed in the foregoing step yields the desired compound of formula VII. This is generally accomplished by reacting the compound of formula VI, wherein R is benzyl, with hydrogen gas at a pressure from about 0 psi to about 2000 psi, preferably about 50 psi, in the presence of a noble catalyst such as palladium, platinum or rhodium. Palladium on carbon or palladium hydroxide on carbon is preferred. The temperature may range from about 20°C to about 80°C, and is preferably about 25°C. The solvent is usually a lower alcohol and is preferably methanol.

When R is (C₁-C₆) alkyl or (C₃-C₆) cycloalkyl, the R group may be removed by reaction with *o*-chloroethylchloroformate (ACE-Cl). (See Olefson *et al.*, *J. Org. Chem.*, **49**, 2081-2 (1984) and Olefson *et al.*, *Pure & Appl. Chem.*, **60**(11), 1715-24 (1988)).

The procedures by which compounds of the formula VII may be used to prepare the quinoline antibiotic having formula I and related azabicyclo quinoline carboxylic acid antibiotics are set forth in United States Patent Application 07/551,212, filed on July 11, 1990 and World Patent Application, WO 91/02526, filed on August 16, 1989 and published on March 7, 1991, both of which are incorporated herein by reference in their entirety.

The antibacterial compound having formula I and the related azabicyclo quinoline carboxylic acid antibiotics that can be synthesized using the methods and compounds of this invention are useful in the treatment of animals, including humans, having bacterial infections. They are useful in treating bacterial infections of broad spectrum, particularly in treating gram-positive bacterial strains.

United States Patent Application 07/551,212 and World Patent Application WO 91/02526 set forth in detail the appropriate dosage ranges and methods of administration of such antibiotic compounds. These references also set forth a method by which the antibacterial activity of such compounds may be determined.

- 5 The following examples illustrate the methods and compounds of the present invention. It will be understood, however, that the invention is not limited to the specific details of these examples.

EXAMPLE 1

1 α , 5 α , 6 α -3-Benzyl-6-nitro-2,4-dioxo-3-azabicyclo[3.1.0]hexane

- 10 To N-benzylmaleimide (24.3 g, 130 mmol) and bromonitromethane (18.2 ml, 260 mmol) was added 250 ml of toluene and the mixture was cooled to 0°C. While stirring vigorously with an overhead stirrer, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (58 ml, 390 mmol) diluted with 200 ml of toluene was added dropwise over a period of 30 min. The reaction was allowed to stir for 2 additional hours at room temperature. The
15 toluene layer was decanted and washed with (2 X 100 ml) 0.1M HCl solution and dried over magnesium sulfate (MgSO₄). Evaporation of the solvent provided 5.4 g of the product which represents a 17% yield. M.P. = 114-115.5°C. ¹H NMR (CDCl₃): 7.31 (m, 5H, aromatics), 4.54 (s, 2H, benzylic), 4.47 (t, 1H, alpha to nitro), 3.35 (d, 2H, 3-ring).

20 EXAMPLE 2

1 α , 5 α , 6 α -3-Benzyl-6-nitro-3-azabicyclo[3.1.0]hexane

- To the 1 α , 5 α , 6 α -3-benzyl-6-nitro-2,4-dioxo-3-azabicyclo[3.1.0]hexane (2 g, 8.1 mmol) from Example 1 in 20 ml of THF was added borane•THF complex (32.4 ml of 1M solution in THF, 32.4 mmol) and the mixture was heated to reflux for 3 hours. The
25 reaction was cooled to room temperature and 10 ml of methanol was carefully added. Heating to reflux was then resumed for 15 min. The solvent was then evaporated and the residual oil was dissolved in 200 ml of CH₂Cl₂ and washed with water (3X100). The organic layer was dried over MgSO₄ and evaporated to provide 1.5 g of the product (light oil) which represents a 90% yield. ¹H NMR (CDCl₃): 7.35-7.19 (m, 5H, aromatics),
30 4.63 (t, 1H, alpha to nitro), 3.59 (s, 2H, benzylic), 3.14 (m, 2H, 5-ring), 2.49 (m, 2H, 5-ring), 2.51 (m, 2H, 3-ring).

EXAMPLE 31 α , 5 α , 6 α -3-Benzyl-6-amino-3-azabicyclo[3.1.0]hexane

To the 1 α , 5 α , 6 α -3-benzyl-6-nitro-3-azabicyclo[3.1.0]hexane (6 g, 27.5 mmol) from Example 2 in 50 ml of ethanol was added zinc dust (18.0 g, 275 mmol). To that
5 was added 150 ml of 1 M HCl solution at such a rate that the temperature of the reaction never exceeded 40°C (1 hour). The reaction was allowed to stir at room temperature for 3 hours after which it was filtered through Celite®. The solvents were then evaporated and the thick white residue was digested with 500 ml of 1M NaOH solution for 3 hours. The mixture was extracted with (2 X 300 ml) CH₂Cl₂ and the
10 combined organic layers were washed with brine (3 X 100) and dried over MgSO₄. Evaporation of the solvent provided 4.06 g of the product which represents a 79% yield. ¹H NMR (CDCl₃): 7.35-7.20 (m, 5H, aromatics), 4.62 (broad singlet, 1H, alpha to nitro), 3.60 (s, 2H, benzylic), 3.14 (m, 2H, 5-ring), 2.52 (m, 2H, 5-ring and m, 2H, cyclopropyl).

EXAMPLE 41 α , 5 α , 6 α -3-Benzyl-6-[(t-butyl formyl)amino]-3-azabicyclo[3.1.0]hexane

To the 1 α , 5 α , 6 α -3-benzyl-6-amino-3-azabicyclo[3.1.0]hexane from Example 3 (3.75 g, 19.9 mmol) in 50 ml of THF was added di-t-butyl dicarbonate (4.78 g, 21.9 mmol) and triethylamine (0.28 ml, 1.99 mmol), and the mixture was allowed to stir for 4 hours. The solvent was then evaporated and 75 ml of methylene chloride (CH₂Cl₂)
20 was added. The mixture was washed with 20 ml of water and dried over MgSO₄. The solvent was evaporated and replaced with 100 ml of hexane. The mixture was heated until all the solids dissolved and 2.5 g of activated charcoal was added and heating was continued for 5 min. The carbon was filtered. Upon cooling the reaction mixture, a solid formed which was filtered and dried in air. The product weighed 5.1 g which
25 represents an 89% yield. M.P. = 131-132°C (white needles). ¹H NMR (CDCl₃): 7.24 (m, 5H, aromatics), 3.54 (s, 2H, benzylic), 3.06 (m, 2H, 5-ring), 2.91 (broad, 1H, alpha to amide), 2.43 (m, 2H, 5-ring), 1.52 (m, 2H, 3-ring).

EXAMPLE 51 α , 5 α , 6 α -[(t-Butyl formyl)amino]-3-azabicyclo[3.1.0]hexane

To 1 α , 5 α , 6 α -3-benzyl-6-[(t-butyl formyl) amino]-3-azabicyclo[3.1.0]hexane from Example 4 (2.0 g, 6.94 mmol) in 50 ml of methanol was added palladium hydroxide on carbon (Pd(OH)₂/C) (50% wet) (1.0 g, 50% by weight). The mixture was hydrogenated at 50 PSI for 6 hours and was then filtered through Celite and the solvent was evaporated to provide 1.36 g of the product in 99% yield. ¹H NMR (CDCl₃): 3.22-2.95

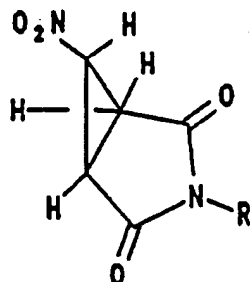
-10-

(m, 4H, 5-ring), 2.61 (broad, 1H, amide), 2.32 (m, 1H, alpha to amid), 1.63 (m, 2H, 3-ring), 1.45 (s, 9H, butyl).

-11-

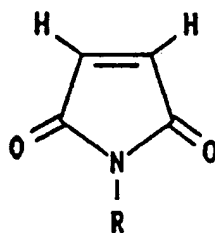
CLAIMS

1. A process for preparing a compound of the formula



(III)

wherein R is (C₁-C₆) alkyl, (C₃-C₈) cycloalkyl or benzyl, wherein the phenyl moiety of said benzyl group may be substituted, optionally, with one or more substituents independently selected from halo, nitro, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, amino and trifluoromethyl, comprising reacting a compound of the formula



(I)

wherein R is defined as above, with a halonitromethane in the presence of a base.

2. A process according to claim 1, wherein the compound of formula III produced is a compound wherein R is (C₁-C₆)alkyl or benzyl.
3. A process according to claim 2, wherein R is benzyl.
4. A process according to claim 1, wherein said halonitromethane is bromonitromethane or chloronitromethane.
5. A process according to claim 1, wherein said process is carried out at a temperature from about -78°C to about 80°C.
6. A process according to claim 1, wherein said process is carried out in a solvent selected from benzene, toluene, dimethylformamide or tetrahydrofuran.
7. A process according to claim 5, wherein said solvent is toluene.

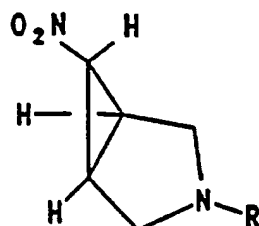
-12-

8. A process according to claim 1, wherein said base is selected from carbonate bases, amino bases and phosphorine amide bases.

9. A process according to claim 8, wherein said base is selected from the group consisting of sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine, triethylamine, guanidine, diisopropylethylamine, tetramethylguanidine, 1,8-diazabicyclo[5.4.0]undec-7-ene and 1,5-diazabicyclo[4.3.0]non-5-ene.

10. A process according to claim 9, wherein said base is 1,8-diazabicyclo[5.4.0]undec-7-ene.

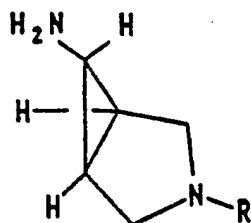
11. A process according to claim 1, further comprising reacting the compound of formula III formed in said process with a reducing agent to form a compound of the formula



(IV)

wherein R is defined as in claim 1.

12. A process according to claim 11, further comprising reacting the compound of formula IV formed in said process with zinc and an inorganic acid to form the corresponding amine having the formula



(V)

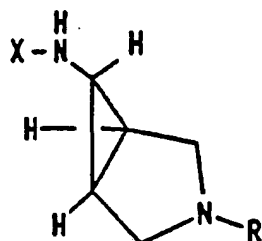
wherein R is defined as in claim 11.

13. A process according to claim 12, wherein said acid is hydrochloric acid or sulfuric acid.

-13-

14. A process according to claim 11, wherein said reducing agent is borane•tetrahydrofuran complex.

15. A process according to claim 12, further comprising adding a nitrogen protecting group to said compound of formula (V) to form a compound of the formula (VI).

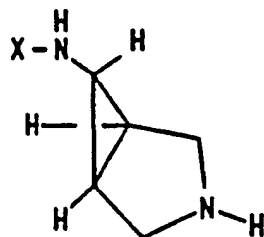


(VI)

wherein R is defined as in claim 12 and X is a nitrogen protecting group.

16. A process according to claim 15, wherein said compound of the formula (V) is reacted with di-t-butyldicarbonate or 2-t-butyloxycarbonyloxymino-2-phenylacetonitrile to form a compound of the formula (VI) wherein X is t-butoxycarbonyl.

17. A process according to claim 15, which produces a compound of the formula VI wherein R is benzyl or substituted benzyl, further comprising subjecting said compound of formula VI to hydrogenolytic removal of the R group to form a compound of the formula

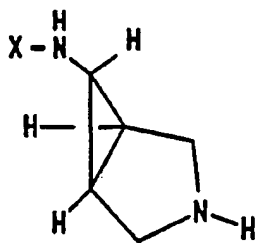


(VII)

wherein X is defined as in claim 15.

18. A compound according to claim 15, which produces a compound of the formula VI wherein R is (C₁-C₆) alkyl or (C₃-C₆) cycloalkyl, further comprising reacting said compound of the formula VI with α -chloroethylchloroformate to form a compound of the formula

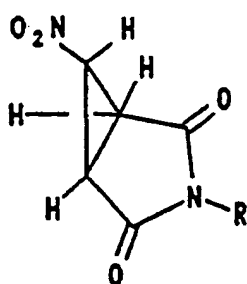
-14-



(VII)

19. A compound having the formula

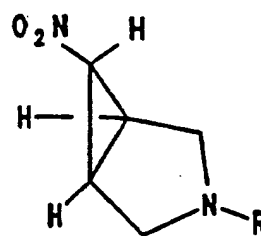
10



15

(III)

or



(IV)

wherein R is (C₁-C₆) alkyl or benzyl, and wherein the phenyl moiety of said benzyl group may be substituted, optionally, with one or more substituents independently selected from halo, nitro, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, amino and trifluoromethyl.

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 C07D209/52		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	EP,A,0 007 128 (SHELL) 23 January 1980 see the whole document ---	11
A	EP,A,0 010 799 (SHELL) 14 May 1980 see page 6 - page 7 ---	1-10
A	EP,A,0 413 455 (PFIZER) 20 February 1991 see page 14 ---	1-19
A	& WO,A,9 102 526 cited in the application ---	
	-/--	
¹⁰ Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "A" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 22 MARCH 1993		Date of Mailing of this International Search Report 25. 03. 93
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer Bernd Kissler

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
L	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY. vol. 114, 1992, GASTON, PA US pages 344 - 345 'Spectroscopic detection of two neutral [CHNO ₂] isomers: Nitrocarbene and Nitrosoformaldehyde' * see p. 344 second paragraph * ---	1-10
A	TETRAHEDRON, (INCL. TETRAHEDRON REPORTS) vol. 46, no. 24, 1990, OXFORD GB pages 8117 - 8130 * see formula 4, page 8117 * ---	19
A	TETRAHEDRON LETTERS. vol. 29, no. 9, 1988, OXFORD GB pages 987 - 990 see the whole document ---	1-10
A	JOURNAL OF ORGANIC CHEMISTRY. vol. 44, no. 8, 13 April 1979, EASTON US pages 1195 - 1199 see the whole document ---	1-10
A	ORGANIC REACTIONS vol. 13, 1963, pages 55 - 90 W. E. PARHAM, E. E. SCHWEIZER 'Halocyclopropanes from halocarbenes' see the whole document -----	1-10

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9300008
SA 68892

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

22/03/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0007128	23-01-80	US-A- 4183857	15-01-80
		AU-B- 527833	24-03-83
		CA-A- 1116612	19-01-82
		CA-A- 1127159	06-07-82
		JP-A- 55011587	26-01-80
		SU-A- 969158	23-10-82
EP-A-0010799	14-05-80	AU-A- 5219579	01-05-80
		AT-T- 1064	15-06-82
		AU-B- 535172	08-03-84
		CA-A- 1116616	19-01-82
EP-A-0413455	20-02-91	WO-A- 9102526	07-03-91
		JP-A- 3086875	11-04-91
		US-A- 5164402	17-11-92